UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/103,745	06/24/1998	SUDHIR AGRAWAL	475.08.642CI	3401

7590 11/13/2006

WAYNE A KEOWN
HALE AND DORR
60 STATE STREET
BOSTON, MA 02109

EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/103,745	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Location of the Application

The location of the application has changed. The application has been docketed to Examiner Louis V. Wollenberger in Art Unit 1635

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-25-2006 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 25 April 20056 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 2 January 2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Double Patenting

Claims 1, and 3-5 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,856,462 for reasons of record, cited in the Office action mailed September 9, 1999.

The previous Action acknowledged Applicant's response to the instant rejection. Applicant has stated that, should any pending claims be indicated as allowable, applicant will file a Terminal Disclaimer disclaiming the portion of the term of the patent beyond the expiration date of U.S. Patent Number 5,856,462.

The instant rejection is maintained until such time.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 3–5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As amended, the claims now include the limitation "wherein the modified CpG is racemic..."

This recitation is unclear in view of the ordinary meaning of the term racemic.

In ordinary usage, the term "racemic" may refer to "a chemical compound that does not deflect or absorb any of the light passing through it. This is because it consists of a precise mixture of dextrorotatory and levorotatory isomers (MSN Encarta Dictionary online). Similarly,

in chemistry, a racemate is a mixture of equal amounts of left- and right-handed enantiomers of a chiral molecule, such a mixture is called racemic (Wikipedia online).

Additionally, in the Remarks filed 4-25-06, Applicant refers to the amendment at page 5 in arguing the applied reference, Cook, and states that Applicant has amended the claims to specify that the remaining modifications are present as "racemic mixtures" of the modified CpG.

However, the amended claims do no reflect that precise amendment. The claims do not contain the word "mixtures." The amended claims recite only "racemic," which is considered to be vague and indefinite when used to modify the term "modified CpG." A "modified CpG" cannot be racemic; a single molecule is either chiral or non-chiral, or may contain regions or centers of chirality or achirality. A single molecule as a whole is either symmetric or asymmetric. To be racemic requires a mixture of at least two molecules.

It is therefore unclear what is meant by the recitation "wherein the CpG is racemic."

Appropriate correction is required.

Claims 1 and 3–5 are further rejected because of the recitation "the modified CpG" in independent claims 1 and 5. There is insufficient antecedent basis for this limitation in the claim.

The limitation appears to be referring to the earlier recitation "a modified CpG-containing phosphorothioate oligonucleotide." However, in this phrase it is unclear whether "modified" refers to the CpG dinucleotide or to the CpG-containing phosphorothioate oligonucleotide.

Thus, at least two alternative interpretations are possible.

Appropriate correction is required.

***

Claim Rejections - 35 USC § 112—New

Claims 1 and 3–5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendment to the claims submitted on 4/25/06, introduces the limitation "wherein the modified CpG is racemic..." into independent claims 1 and 5.

MPEP §2163, Section II, Part A, states, in part, that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed, *Wertheim*, 541 F.2d at 262, 191 USPQ at 96; however, with respect to newly added or amended claims, applicant should show support in the original disclosure for the new or amended claims.

MPEP §2163.05 states in part that each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure.

In the instant case, Applicant states (Remarks, page 5) that the amendments are supported implicitly throughout the specification because the person of ordinary skill in the art would recognize that the failure to teach extraordinary stereospecific isomers of chiral alkylphosphonate, phosphotriester and phosphoramidate centers, along with the contrasting specific teaching of "stereospecific phosphorothioate" chiral centers, implicitly indicates that the indicated CpG modifications cover racemic mixtures of the chiral compounds.

Applicant's remarks have been fully considered but are not found persausive.

A review of the application fails to find clear, implicit or explicit antecedent support for the instant limitation.

Applicant appears to be arguing that the absence of any disclosure concerning the stereospecificity of the alkylphosphonate, phosphotriester and phosphoramidate centers implies that stereospecificity is not a factor essential to the instant invention, nor would one of skill in the art consider it to be a factor. Presumably, based on the absence of such disclosure, one of skill in the art would therefore consider such modifications to be directed to "racemic" compounds.

This argument is not persuasive.

The written description guidelines are clear on this point: What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. Stated another way, the description need only describe in detail that which is new or not conventional (MPEP §2163).

In the instant case, there is no disclosure either in the instant application or the parents that would indicate to one of skill in the art at the time the application was effectively filed that racemic alkylphosphonate, phosphotriester and phosphoramidate modifications were a new, non-conventional, or essential feature common to the genus of CpG-containing oligonucleotides that have reduced side effects, as now claimed.

In fact, there is no disclosure teaching for or against the use of racemic alkylphosphonate, phosphotriester and phosphoramidate centers in CpG-containing phosphorothioate oligonucleotides, there is only the teaching that oligos comprising these modifications have reduced side effects.

Thus, absent such disclosure, one of skill would be informed by the prior art (Cook, for example, cited in the previous Action) that chirally pure, phosphorothioate modified oligonucleotides may be more potent than racemic mixtures. One of skill in the art could just as easily surmise that the instantly claimed oligonucleotides should be synthesized as stereochemically pure oligonucleotides.

For example, Cook teaches that "Since they exist as diastereomers, phosphorothioate, methylphosphonate, phosphotriester or phosphoramidate oligonucleotides synthesized using known, automated techniques result in racemic mixtures of Rp and Sp diastereomers at the individual phosphorothioate, methylphosphonate, phosphotriester or phosphoramidate linkages. Thus, a 15-mer oligonucleotide containing 14 asymmetric linkages has 2.sup.14, i.e. 16,384, possible stereoisomers. Accordingly, it is possible that only a small percentage of the oligonucleotides in a racemic mixture will hybridize to a target mRNA or DNA with sufficient affinity to prove useful in antisense or probe technology" (see Cook, US Patent 5,212,295, Col. 2, lines 15-30).

Cook also teaches at column 4, top, that "...little is known concerning the effects of differing chirality at the phosphorus linkages. It would therefore be of great advantage to provide oligonucleotides having phosphorous linkages of controlled stereochemistry."

These teachings are clearly directed to antisense oligonucleotides in general, regardless of of sequence.

Accordingly, Applicant has not provided any evidence that they were in possession of the genus of CpG-containing oligonucleotides comprising racemic backbone modified CpG centers such as those now recited that have reduced side effects.

Accordingly, the instant claims as a whole are rejected for lack of written description support because the limitation added by amendment on 4-25-06 is not supported expressly, implicitly, or inherently supported in the originally filed disclosure.

Claim Rejections - 35 USC § 102—withdrawn

The rejection of Claims 1 and 3-5 under 35 U.S.C. 102(b) as being anticipated by Cook (U. S. Patent Number 5,212,295) is withdrawn in view of Applicant's amendments to the claims.

Cook does not teach phosphorothioate oligonucleotides comprising a modified CpG that is "racemic."

Cook teaches the synthesis of chirally pure, backbone modified antisense oligonucleotides.

Claim Rejections - 35 USC § 102—new

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

As now amended, Claims 1 and 3–5 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550), as evidenced by Cook (U.S. Patent 5,212,295).

Agrawal et al. disclose self-stabilized, hairpin oligonucleotides comprising target hybridizing and self complementary regions that form a totally or partially double stranded structure that is resistant to nucleolytic degradation (pg. 5, lines 13-17, 25–30). The self-

stabilized oligonucleotides are specifically designed for inhibiting gene expression in vitro and in vivo by inducing RNase H-mediated cleavage of a target mRNA (pages 5-6).

At page 8, it is taught that the target hybridizing and a self complementary regions of the oligonucleotide can be composed of ribonucleotides, deoxyribonucleotides, or both, with ribonucleotide and/or deoxyribonucleotide monomers being connected together via 5' to 3' linkage (pages 8–16, for example). Additionally, it is taught that the oligonucleotide may include modified nucleic acid bases and/or sugars as well as molecules having added substituents, such as diamines, cholesteryl, or other lipophilic groups.

At page 16 it is taught that the self-complementary region may contain ribonucleotides, deoxyribonucleotides, analogs of ribonucleotides or deoxyribonucleotides having artificial linkages, or combinations of any of the above. It is further taught that the ability to activate RNase H is not important for the self-complementary region, so nucleotides having artificial linkages that do not activate RNase H can be used in this region without diminishing the effectiveness of the oligonucleotide. Thus, in addition to phosphodiester and phosphorothioate or phosphorodithioate linkages, this region may also or alternatively contain phosphoramidate (including N-substituted phosphoramidates), alkylphosphonate, alkylphosphonothioate linkages as well as non-phosphate containing linkages, such as sulfone, sulfate, and keto linkages.

Agrawal et al. teach and claim that their self-stabilized, backbone modified antisense oligonucleotides may be used for therapeutic purposes to inhibit gene expression in a human or other mammal, such as, for example, to treat a disease arising from a virus or pathogenic organism infection (see claim 19, for example, and page 18).

Agrawal et al. show a number of representative embodiments, including as series of hairpin, CpG-containing oligonucleotides said to have anti-HIV activity and which are directed to a portion of the gag region of the HIV-1 genome (see Fig. 5 and Examples 1-3, pp. 20-28).

While Agrawal et al. do not specifically teach that the backbone modifications should be specifically incorporated into CpG spots, Agrawal et al. teach and suggest the general use of phosphorothioate and other such backbone modifications as now recited for incorporation into virtually any self-stabilized antisense oligonucleotide of any sequence, including the CpG-containing, anti-HIV embodiments represented. Moreover, Agrawal et al. teach and suggest the combined use of backbone modifications throughout the oligonucleotide as necessary to render the oligonucleotide more stable.

And while Agrawal et al. do not teach that such modifications reduce the side effects of oligo therapy, or render the oligonucleotides less immunostimulatory, this feature is an inherent aspect of the oligonucleotides taught by Agrawal et al.

It is noted that Agrawal et al. do not emphasize or teach the importance of stereospecificity with regard to the backbone modifications suggested for incorporation into antisense oligonucleotides. Therefore, based on Applicant's earlier argument (described above), one of skill may infer from Agrawal et al. that such considerations are not essential, and that such backbone modifications may be synthesized as a racemic mixture, as evidenced by the prior art.

Cook, for example, referring to the state of the art of oligonucleotide synthesis in general, teaches that "the sequence-specific phosphorothioate, methylphosphonate, phosphotriester or

phosphoramidate oligonucleotides obtained utilizing known automated synthetic techniques have been racemic mixtures (column 3).

Accordingly, Agrawal et al. anticipates the instant claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571)272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Louis Wollenberger
Examiner, Art Unit 1635
November 6, 2006

SEAN McGARRY
PRIMARY EXAMINER
1635